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FURADANTIN

Nitrofurantoin (Furadantin-Eaton) is an antibacterial drug recommended for oral use in the treatment of acute and chronic urinary-tract infections. It is by no means new; it merits review, however, because of its bacteriostatic and bactericidal effectiveness against a very wide range of both gram-positive and gram-negative organisms, its relative freedom from toxicity when used orally, and the fact that its use does not encourage the growth of resistant strains. These qualities give it a special clinical usefulness for those urinary-tract infections in which the sulfa drugs and antibiotics are not suitable.

Furadantin is active against a great variety of gram-positive cocci, including some resistant strains of Staphylococci, and against many gram-negative bacilli, including E. coli, Proteus species, Klebsiella pneumoniae (Friedlander's bacillus), and Aerobacter aerogenes. Most strains of Pseudomonas aeruginosa (B. pyocyaneus) are resistant to its action as are the tubercle bacillus, the spore-forming anaerobes (such as Clostridia), Rickettsia and many pathogenic fungi and viruses.

Furadantin is almost completely absorbed after oral administration, as indicated by the fact that about half of the dose is excreted in the urine, with only negligible amounts in the feces. Nevertheless, laboratory determinations have failed to show its presence in significant amounts in the blood. This characteristic makes oral dosage useless for systemic infections; the drug is primarily a urinary antiseptic, suppressing surface but not deep tissue infections. (To make the drug useful for systemic infection, the manufacturer developed an intravenous preparation containing Furadantin in polyethylene glycol as a solvent. While no untoward effects were evident at first, subsequently some of the patients receiving this preparation developed severe metabolic acidosis. This was attributed to the solvent, and the preparation has been withdrawn while a safer vehicle is sought.)

DOSAGE - In the treatment of acute urinary-tract infections, 50- to 100-mg. doses four times a day are recommended for adults. A. Welling, et al. (J. Urology, 77:773, 1957), showed that the 100-mg. dose is generally necessary only with resistant gram-positive organisms. Fifty-mg. doses appear to be just as effective for most other urinary infections, and the smaller doses are less likely to produce gastrointestinal irritation. If the response to the smaller dosage

is inadequate, it can be increased. In many instances, 50-mg. doses only twice a day are sufficient to sterilize the urine. Treatment should be continued for at least three to seven days after the urine becomes sterile.

Furadantin not infrequently causes nausea and vomiting, especially with larger doses; reduction of dosage usually results in prompt alleviation of symptoms. In rare cases, Furadantin causes skin sensitization, leukopenia and hemolytic reactions, as well as diffuse erythematous maculo-papular eruptions. Hemolytic anemia from Furadantin therapy seems more prone to occur in Negro patients. Its administration is reported not to result in any marked decrease in intestinal bacterial count, change of flora or excessive multiplication of fungi.

USES OF FURADANTIN - Furadantin is promoted as the drug of first choice in urinary-tract infections. For acute urinary infections, it is a valuable addition to a physician's resources, ranking with sulfa drugs and broad-spectrum antibiotics. Furadantin is also valuable in preventing urinary infections in catheterized patients. For chronic infections, where there is urinary stasis, clinical results are often disappointing even when the responsible organism is sensitive to the drug used. Persistence of an infection in spite of normally adequate treatment suggests the presence of a stone, surgical or congenital anomaly, or a neurogenic cause of urinary stasis. Treatment of these conditions may be necessary before the infection can be controlled. Dr. Ernest Jawetz and his associates carefully studied 32 patients with chronic urinary-tract infections and concluded that a urinary antiseptic such as Furadantin ". . . no matter how strongly antibacterial its action in the urine or how long it is taken, is not likely to eradicate the infection in the interstitial tissue of the kidney in chronic pyelonephritis." (E. Jawetz, et al., AMA Arch. of Int. Med., 100:549, 1957.)

Furadantin may, however, have considerable value even in cases where bacteria cannot be eliminated from the urine permanently. Given a sensitive organism, its administration in low dosage (50 mg. twice a day) for prolonged periods may keep the urine sterile, and suppress symptoms; and it may possibly influence favorably the tissue infection in the urinary tract. Renal function may also improve during such therapy.

FUROXONE

Physicians are being advised to treat "acute diarrheal disease problems" with Furoxone Liquid (Eaton's brand name for furazolidone with kaolin and pectin. Furazolidone is a nitrofuran related to nitrofurantoin [Furadantin]). Unlike Furadantin, a significant amount of Furoxone remains in the feces; hence its proposed use in intestinal infections. The claim is made that Furoxone "rapidly destroys bacterial pathogens. . . succeeds where others fail against the enteric 'problem pathogens' - increasingly prevalent, refractory strains of Staphylococcus, Escherichia, Salmonella and Shigella."

Diarrhea is a symptom with many causes. In a study of diarrheal disease in children, M. R. Alvarez and A. Sabin (JAMA, 167:155, 1958) found that most of the infections responsible for the diarrhea were caused by viruses, so that

no antibacterial agent would be of any value. Furthermore, except in epidemics, or in areas with the most primitive sanitation facilities, infections with Salmonella and Shigella are uncommon; enterotoxic strains of Staphylococcus aureus and Escherichia coli are also relatively uncommon causes of diarrhea. Even with these organisms, however, there is no clear evidence that Furoxone is particularly effective.

CLINICAL AND LABORATORY EVIDENCE - In a published series of 30 Mexican cases of "acute bacterial diarrheal syndrome" cited in Furoxone literature, either Salmonella or Shigella was the responsible organism in 22. It is claimed that Furoxone effected cures in 17 of the 22 cases; but intestinal infections caused by the great majority of species of Salmonella and Shigella are usually mild, of short duration and generally self-limiting, so that spontaneous cure without treatment is common. As the report shows, in five cases the infection continued despite the use of Furoxone.

Laboratory determinations are cited to show effective in vitro antibacterial activity against Shigella and Salmonella, but correlation between laboratory findings and therapeutic effectiveness is far from absolute. For example, many strains of Salmonella are more sensitive to the tetracyclines and to streptomycin than to chloramphenicol (Chloromycetin--Parke-Davis) in the laboratory, yet clinically Chloromycetin has been found more effective than the others.

To be sure, there is room for a new agent which will be consistently effective against the more troublesome strains of Salmonella. While Chloromycetin must still be considered the first choice for the treatment of such infections, relapses occur in a considerable proportion of cases in spite of intensive and prolonged treatment, and sometimes while the patient is still receiving the drug. Furthermore, Chloromycetin, like all the other currently available agents, is not very effective in clearing up the carrier state which poses such a serious epidemiological problem after many Salmonella infections. On the basis of clinical trials and reported experience to date, reliance can hardly be placed on Furoxone to cure Salmonella infections, prevent relapses, or clear up the carrier state.

TOXICITY OF FUROXONE - The claim that no toxicity has been reported from the use of Furoxone is not very meaningful, since it is based on limited experience. The manufacturer's literature states that nausea, headaches, malaise and emesis may occur in a small percentage of patients, and that "mild sensitization" in the form of a vesicular or morbilliform rash has occurred in "a few cases."

In the United States, most cases of acute diarrhea are mild and self-limiting, and respond readily to symptomatic measures such as high fluid intake, a low-residue diet and, where needed, either tincture of opium or Kaolin Mixture with Pectin (N. F.). If the diarrhea lasts more than 48 hours and is accompanied by fever or by blood in the stools, a stool culture may be necessary to identify the pathogens. For severe Shigella infections, the sulfonamides are the drugs of choice. For severe Salmonella infections, as already indicated, Chloromycetin is the drug of choice.

DARVON

Propoxyphene HCl (Darvon-Lilly), offered as a substitute for codeine, has been judged non-addicting by the Committee on Drug Addiction of the National Research Council; and accordingly, the U. S. Bureau of Narcotics has not classed it as an addicting analgesic. Darvon is, therefore, superior in this respect to codeine, which has very mild addicting properties.

While the AMA Council on Drugs (JAMA, 166:1483, 1958) describes Darvon and codeine as being approximately equal in potency, in onset and duration of effect, and in usefulness for the same types of pain, only one major controlled clinical trial has been reported (from the Lilly Laboratory for Clinical Research). In this trial, patients were given aspirin as well as Darvon, codeine and placebos. The data on the analgesic effects of aspirin as compared with Darvon and with codeine were not included in the analysis of results. Two investigators consulted by The Medical Letter expressed doubt that Darvon is as effective as codeine; one of these questioned whether, indeed, it has been shown to be more effective than either codeine or aspirin. Unlike codeine, Darvon has little or no antitussive activity, and it cannot be injected because it causes local irritation.

SIDE EFFECTS - Skin rashes as well as nausea and vomiting have been noted with average doses of the drug, though the limited studies thus far indicate that nausea and vomiting may be less frequent with Darvon than with codeine. Much longer experience is needed for knowledge of the range and severity of the drug's side effects. Since the problem of addiction is a minor one with codeine, the chief advantage of Darvon to physicians probably lies in the fact that the drug can be prescribed by phone (it does not require a narcotics license number). Depending largely on the quantity purchased, a 32-mg. pulvule of Darvon costs the patient about 6¢ to 9¢. A 32-mg. tablet of codeine costs about 7¢ to 12¢.

NOTE ON SINGOSERP

In a preliminary review of syrosingopine (Singoserp-Ciba) in the April 17th issue of The Medical Letter, a report by Barbour, et al. in the American Journal of Cardiology was given as the source of data on the incidence of side effects with Singoserp. The source was not the Barbour report, however, but a pamphlet on Singoserp published by Ciba, which states, "More than 80 per cent of [over 2000] reported cases have been entirely free of objectionable side effects while receiving this drug..." Depression was noted "in a small percentage of cases."

The Ciba data appear to be based almost entirely on uncontrolled observations, most of them reported in personal communications. It is to be hoped that carefully controlled double-blind studies will be carried out with a large enough number of patients, and over a long enough period, to permit more confident evaluation of the claims than is now possible, as to both therapeutic effectiveness and side effects. Neither the studies cited by Ciba nor a more recent study (JAMA, 169:1609, Apr. 4, 1959) used adequate control techniques. Such techniques are essential where subjective factors are important, as in hypertension.

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